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Complications in 100 Living-Liver Donors

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Objective
A review of 100 living-liver donors was performed to evaluate the perisurgical complications of the procedure and thus to help quantify the risks to the donor.

Summary Background Data
Despite the advantages of living-donor liver transplantation (LDLT), the procedure has received criticism for the risk it imposes on healthy persons. A paucity of data exists regarding the complications and relative safety of the procedure.

Methods
One hundred LDLTs performed between November 1989 and November 1996 were reviewed. Donor data were obtained by chart review, anesthesia records, and the computerized hospital data base. Patient variables were compared by Fisher's exact test and the Student's t test.

Results
There were 57 women and 43 men with a median age of 29. Donors were divided into two groups: group A (first 50 donors), and group B (last 50 donors). There were 91 left lateral segments and 9 left lobes. There were no deaths. Fourteen major complications occurred in 13 patients; 9 occurred in group A and 5 in group B. Biliary complications consisted of five bile duct injuries (group A = 4, group B = 1) and two cut edge bile leaks. Complications were more common in left lobe resections (55%) than in left lateral segment grafts (10%). Minor complications occurred in 20% of patients. A significant reduction in overall complications (major and minor) was observed between the groups (group A, n = 24 [45%] *vs.* group B, n = 10 [20%]). In addition, surgical time and hospital stay were both significantly reduced.

Conclusions
Although the procedure is safe, many LDLT donors have a perisurgical complication. Surgical experience and technical modifications have resulted in a significant reduction in these complications, however. To minimize the risks for these healthy donors, LDLT should be performed at institutions with extensive experience.

Living-donor liver transplantation (LDLT) was first reported in two patients by Raia et al.[1] in 1989. Both recipients died shortly after the procedure of medical complications but lived long enough to establish the technical feasibility of the procedure. This was soon followed by a report from Strong et al.[2] in Australia, where the first successful transplant of a child using its mother's left lobe was performed in July 1989. Before the initial reports by Raia and Strong, an extensive ethical appraisal of the concept of LDLT was in progress at the University of Chicago, where clinical ethicists and transplant physicians convened a year-long series of seminars and discussions open to the entire university community.[3] From these meetings, a proposal was submitted to the institutional review board and a successful LDLT was performed by Dr. Christoph Broelsch in November 1989. This initiated the systematic use of LDLT in children with end-stage liver disease.[4,5] Between November 1989 and July 1996, 100 LDLTs were performed, with 1-year patient and graft survival rates of 88% and 72%, respectively (unpublished observations). Similar results have been reproduced worldwide, confirming the effectiveness of the procedure.[6–10]

LDLT has several advantages for the child and the transplant population as a whole. First, it increases the number of organs directly available for the pediatric population. Second, most recipients receive their transplant on an elective basis and thus should incur lower morbidity and mortality

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rates and decreased overall cost. Third, the minimal cold ischemia time and the use of healthy donors may contribute to the absence of primary nonfunction. Finally, there is a theoretical immunologic advantage of receiving a living-related organ, as suggested by the lower incidence of steroid-resistant rejection compared with cadaveric liver transplants.[11]

Despite the impressive results of LDLT, considerable debate persists concerning donor safety. Risks to the donor include those associated with invasive presurgical testing and the surgical procedure. These risks are accepted by the potential donors in exchange for the knowledge that a child's life may be saved without the uncertainty of the cadaveric waiting list.

METHODS

One hundred LDLTs performed between November 1989 and November 1996 were reviewed. Donors were divided into two groups: group A (first 50 donors) and group B (last 50 donors). Donor data used for analysis were obtained by chart review, anesthesia records, and the computerized hospital data base. The first 20 donors underwent surgery under a strict investigational review board protocol that required a 2-week consent process in accordance with the ethical standards of the Committee on Human Experimentation at the University of Chicago. Complications were classified as major if they required surgical or invasive intervention. All other complications were classified as minor. Patient variables were compared by Fisher's exact test and the student's t test performed using In Stat version 2.0 (GraphPad Software, San Diego, CA). For all tests, a p value < 0.05 was considered significant.

Presurgical Evaluation of Donors

Eligible donors included those between the ages of 18 and 55 years who were ABO blood type compatible with the recipient. Acute or chronic medical illness was excluded by a detailed history and physical examination, and all donors were screened for transmissible viral illness by serologic testing. All donors had normal liver function and no history of liver disease. Psychosocial assessment of the donor and the family was performed by a social worker and a donor-advocate physician who was not a member of the transplant team. All potential donors then underwent volumetric computed tomography scanning to assess liver volume and to exclude unsuspected intraabdominal pathology, and hepatic angiography to detect anomalous vasculature incompatible with donation. Percutaneous liver biopsy was not routinely performed in patients to assess steatosis. However, we currently perform this procedure for all female donors because they have a higher probability of having unsuspected hepatic steatosis. For parents of children undergoing transplantation for Alagille's syndrome, endoscopic retrograde cholangiopancreatography (ERCP) is performed to ensure the adequacy of the biliary tract. All donors were offered the opportunity to provide autologous blood for transfusion if required.

Donor Surgical Procedure

This is described in detail elsewhere.[12,13] Briefly, the abdomen is entered through a bilateral subcostal incision with a vertical midline extension. The falciform, left triangular, and gastrohepatic ligaments are divided with electrocautery. The left hepatic artery is dissected, exposing the left portal vein lying posteriorly. Branches from the left portal vein entering segments 1 and 4 are ligated and divided. The round ligament is retracted to the left, and the vascular and biliary structures to segments 1 and 4 arising from the left hepatic artery and left bile duct are ligated and divided. The left hepatic duct is then transected close to the parenchyma of the left lateral segment (LLS) and the distal end is oversewn. Finally, the parenchymal dissection is performed using electrocautery with suture ligation of large vessels. After completion of the parenchymal dissection, the LLS is attached to the donor only by the left hepatic artery, left portal vein, and left hepatic vein. These are transected, and the liver is transferred to the back table for flushing of the hepatic artery and portal vein with preservation fluid at 4°C. A segment of donor saphenous vein is harvested from the left groin in the event that an arterial conduit is needed in the recipient.

Recent changes in the surgical technique have included transection of the left hepatic duct close to the parenchyma of the LLS to minimize the chance of encroaching on the confluence of the right and left hepatic ducts and to minimize bile duct ischemia. Similarly, the left hepatic artery is transected away from the bifurcation, resulting in a left hepatic artery that is shorter than in earlier cases. The donor left hepatic artery is anastomosed to the recipient's common hepatic artery using the operating microscope, thus eliminating the routine use of a conduit.

In our early experience, all living donors were closely monitored for 24 hours in a stepdown unit. However, as experience and confidence grew, patients were subsequently admitted after surgery to a regular hospital bed with routine monitoring. After surgery, all patients received patient-controlled analgesia by pump infusion for 48 to 72 hours and then converted to oral pain medication. Nasogastric tubes were removed on postsurgical day 1 and clear liquids were begun. Early ambulation and incentive spirometry were encouraged to minimize atelectasis. Pneumatic compression boots were used on all patients during and after surgery until patients were fully mobile. Drains were removed when the patient was tolerating a regular diet without evidence of biliary leak.

RESULTS

Of the 100 donors reviewed, there were 57 women and 43 men with a median age of 29 years (range 18 to 54 years).

Table 1. MANAGEMENT AND OUTCOME OF MAJOR COMPLICATIONS IN 100 LIVING-LIVER DONORS

Donor No.	Type	Complication	Outcome/Management
1	LL	Retractor injury to spleen	Splenectomy
1	LL	Bile leak from stump of LHD	USS guided drainage
2	LL	Abscess at cut edge	CT guided drainage
3	LLS	Bile leak from cut edge	Operative drainage
19	LLS	Injury to RHA	Repaired-thrombosed postoperative
32	LLS	Injury to CBD	Repair/T-tube
40	LLS	Wound dehiscence	Wound reclosed
45	LLS	Injury to segment 4 bile duct	Operative repair/drainage
46	LLS	LHD transected too close to RHD	Choledochojejunostomy
60	LLS	Bile leak from caudate	Operative repair/drainage
73	LLS	Perforated duodenal ulcer	Omental patch repair
81	LL	Gastric outlet obstruction	Endoscopic dilatation
87	LLS	Wound dehiscence	Wound reclosed
94	LL	Suspected narrowing of CBD	T-tube placed

LL = left lobes; LLS = left lateral segments; LHD = left hepatic duct; RHA = right hepatic artery; CBD = common bile duct; RHD = right hepatic duct.

Donor weights ranged from 47 to 110 kg, with a mean of 70.4 ± 12.3 kg. The relationships of the donors to the recipients were as follows: mother (n = 54), father (n = 35), uncle (n = 4), aunt (n = 3), close friend (n = 3), and grandmother (n = 1). These 100 donors yielded 91 LLS and 9 left lobes (LL). Group A had 4 LL and 46 LLS, group B 5 LL and 45 LLS. No complications occurred secondary to computed tomography scanning, angiography, liver biopsy, or ERCP.

The mean time from skin incision to closure was 276 ± 73 minutes (range 120 to 580 minutes). There was a significant reduction in mean surgical time between group A and group B (312 ± 75 minutes *vs.* 234 ± 43 minutes, $p < 0.001$, respectively). Cell saver blood was used in 87 donor hepatectomies. The mean return of cell saver blood to the patient was 395 ± 248 cc (range 75 to 1450). Five patients received heterologous blood transfusions (four in group A *vs.* 1 in group B, p = NS). Four patients each received 1 unit of previously donated autologous blood. There was no significant difference between the groups in the mean transfusion requirements (411 cc in group A *vs.* 434 cc in group B, p = NS). No cases of transfusion-associated viral transmission have been reported. The mean hospital stay was 6.8 ± 2.7 days (range 4 to 20 days). A significant reduction in mean hospital stay was noted between the groups (7.6 ± 3.1 days in group A *vs.* 6 ± 2 days in group B, $p < 0.001$).

Surgical and Postsurgical Complications

A total of 34 complications (major and minor) occurred in 100 liver donors, with a significant reduction occurring over time (24 in group A *vs.* 10 in group B, $p < 0.005$. Fourteen major complications occurred either during the procedure or in the perisurgical period (Table 1). Of these, nine occurred in group A and five in group B (p = NS). Four of the 14 major complications occurred in the first three patients. The 14 major complications comprised 7 biliary complications, 1 hepatic artery thrombosis, 1 intra-abdominal abscess, 1 splenectomy, 1 perforated duodenal ulcer, 1 gastric outlet obstruction, and 2 wound dehiscences. Five of these complications required further surgery in the immediate postsurgical period. Two patients required laparotomy for bile leaks, two patients required fascial reclosures for wound dehiscence, and one patient required an omental patch for a perforated duodenal ulcer.

Biliary complications consisted of five bile duct injuries (four in group A *vs.* one in group B, p = NS) and two cut edge bile leaks that required percutaneous drainage. Descriptions of the five bile duct injuries are as follows: bile leak from the left hepatic duct stump requiring percutaneous drainage, partial transection of the common bile duct repaired over a T tube, an injury to a segment 4 bile duct repaired during surgery that later required percutaneous drainage for an infected bile leak, and two instances in which the left hepatic duct was transected too close to the common bile duct. Direct closure over a T tube was used without sequelae in one instance and a choledochojejunostomy was performed in the other instance, also without sequelae. The hepatic artery thrombosis was secondary to a right hepatic artery injury that was repaired during surgery but on postsurgical duplex scanning was found to be thrombosed. No late sequelae have occurred in the 6-year follow-up of this patient. Delayed gastric emptying was seen in four patients in the immediate postsurgical period. This problem failed to resolve in one of these patients with conservative management and required endoscopic pyloric dilatation.

A single case of a penetrating peptic ulcer, causing hemetemesis, occurred when a donor was readmitted 18 days after surgery for upper gastrointestinal hemorrhage.

Table 2. MINOR COMPLICATIONS IN 100 LIVING-LIVER DONORS

Group A	Group B
Urinary tract infection (n = 3)	Postoperative ileus (n = 3)
Postoperative ileus (n = 3)	Admission for nonspecific abdominal pain (n = 2)
Admission for nonspecific abdominal pain (n = 2)	Pneumonia (n = 1)
Wound infection (n = 2)	Urinary retention (n = 1)
Rash from medication (n = 2)	
Pneumothorax (n = 1)	
Pneumonia (n = 1)	
Urinary retention (n = 1)	

This patient had been taking nonsteroidal antiinflammatory medication for postsurgical pain. Endoscopy failed to define the site of bleeding, and the patient was taken to the surgical suite, where a perforated duodenal ulcer was found to have penetrated into the cut edge of the liver. The bleeding vessel on the cut surface was oversewn and the ulcer was repaired with an omental patch.

Minor complications occurred in 20% of patients and included two wound infections, two adverse reactions to medications, one case of urinary retention, four episodes of prolonged ileus, one pneumothorax, four urinary tract infections, two cases of pneumonia, one case of mild neurapraxia, and three others, all of which were managed conservatively (Table 2).

A significant reduction in overall complications (major and minor) was observed between group A and group B ($p < 0.005$; Fig. 1). Major complications and biliary complications were reduced; however, the reductions did not reach statistical significance. Complications were more common in LL resections (5/9; 55%) than in LLS grafts (9/91; 10%) ($p < 0.002$).

DISCUSSION

Despite the impressive results and obvious advantages to the child and the transplant population as a whole, the concept of LDLT has received criticism for the risk it imposes on an otherwise healthy person who may find him- or herself obligated to undergo surgery for a sick child. These risks include those associated with the presurgical evaluation of the donor (*e.g.*, angiography and liver biopsy) as well as the risks of surgery, which include all the known complications of a major hepatic resection.

The concept of living donation has been applied to several different solid organ transplants, including kidney, lung,[14] small intestine,[15] and pancreas.[16] Living-donor kidney transplantation (LDKT) is the most commonly performed living-donor transplant and is now routinely performed worldwide, with long-term graft survival exceeding that for cadaveric transplants.[17] Advocates of LDKT justify its use by pointing to the shortage of cadaveric organs and the low morbidity and mortality rates incurred by the donor. The risks of donation in this context have been estimated from large numbers of donors worldwide and suggest a major morbidity rate of 0.9% to 7%[18] and a mortality rate of 0.03%.[19] In addition, although some concerns have been raised about hypertension and proteinuria, the long-term risk to donors after nephrectomy appears to be small, and donors are reported to enjoy a good quality of life. Unfortunately, no case-controlled longitudinal studies are available, nor are there any national registries for follow-up of living-kidney donors.

Data about the morbidity and mortality rates from the donation of organs, other than kidneys, are difficult to assess because of the small numbers involved. In one report from the University of Minnesota, 78 living-donor pancreas transplants were reported over a 27-year period with a major complication rate of 13%.[20] In addition, three of the donors developed abnormal results on glucose tolerance tests during follow-up, suggesting that these donors may develop diabetes in the future.

Data about the perisurgical complications and long-term outcome of donors in living-liver donors are sparse; again, there is no national registry that follows these persons. Further, the numbers reported in most series are too small to allow conclusions to be made concerning the risk of the procedure. Extrapolation from the data concerning liver resections for benign and malignant disease suggests that the mortality rate in persons without cirrhosis should approach zero in experienced hands, irrespective of the type of resection.[21,22] Clearly, all forms of living-donor transplantation are subject to varying degrees of complications and death, depending on the complexity of the procedure, and despite good intentions and experienced hands, there can be no argument that a finite risk of death to the donor exists. Yamaoka et al.[7] reported their complications in 100 living-liver donors as four bile leaks, one case of esophagitis, seven cases of gastritis, and three gastroduodenal ulcers, all of which resolved without long-term sequelae. Sterneck et al.[23] reported seven major complications in 35 living-liver donors (20%), which included one death from a pulmonary embolism on day 2 after an uneventful surgery.

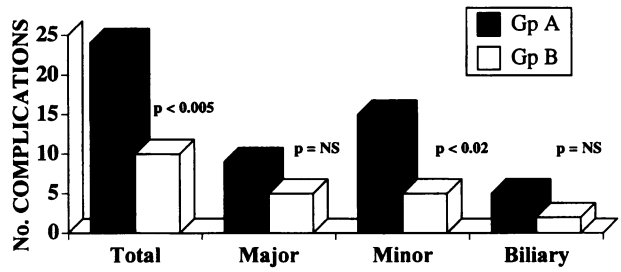

Figure 1. Complications in group A (first 50 donors) *vs.* group B (subsequent 50 donors). Major complications include all biliary complications, which are also shown separately.

The decision to use living donors for both kidney and pancreas transplantation is considered ethically acceptable because of both the shortage of cadaveric organs and the superior function of the grafts from living donors. However, unlike kidney and pancreas transplantation, both of which have alternative medical treatments that would potentially allow cadaveric transplantation, liver transplantation is performed for a life-threatening illness for which there is no other form of medical treatment. Thus, if one accepts the use of living donors for either kidney or pancreas transplantation, the use of living liver donors for end-stage liver disease is even better justified.

It appears that although all living donors are at risk for complications and death at the time of the surgery, the long-term risks may differ from those of other organs. Kidney donors clearly have a risk of hypertension and proteinuria many years after donation, but it is unclear whether this will translate into poor renal function in the future. Similarly, donation of segmental pancreas grafts has raised some concern over the possibility of developing diabetes as a consequence of the reduced islet cell mass. The morbidity rate of living-liver donation appears to be almost entirely related to the perisurgical period. Long-term complications, to our knowledge, have not been reported in living-liver donors. The potential for long-term complications in donors who had major complications clearly exists, especially from injuries involving the biliary tract. In our series, these complications appear to have been effectively managed at the time of surgery, and long-term complications in these patients have not occurred on long-term follow-up (unpublished observations). This suggests that although complications may occur as a consequence of the procedure, they can be treated effectively and the donor can return to a normal life. In addition, it is unlikely that long-term sequelae will occur related to the reduction in liver cell mass that occurs with liver donation. This can be supported by studies that demonstrate long-term preservation of liver function in the face of partial hepatectomy. Indeed, left lateral segmentectomy has been shown to have no significant functional or physiologic effects, provided that the resection does not exceed 40% of the liver mass; in many instances, a patient will tolerate a 50% resection and regenerate fully.[24,25] Indeed, liver regeneration has been shown to occur in living-liver donors, although not as quickly as in the recipient.[26]

The complications reported in this study represent those from the first center to develop a fully structured LDLT program after extensive ethical issues were addressed, and with the knowledge that the team was experienced in segmental resection and grafting. The evolution of LDLT at the University of Chicago has resulted in changes in the management of these donors, leading to a significant reduction in overall complications, surgical time, and hospital stay.

Results from this retrospective analysis show that 34% of all living-liver donors had a complication of some magnitude. These complications varied in severity: approximately 60% were minor and not life-threatening. Most complications did not require surgical intervention, and no long-term sequelae or deaths have been reported. Major complications occurred in 14% of all patients. Many of these complications occurred early in the pioneering experience with this procedure—4 of the 14 complications occurred in the first three patients. Comparison between group A and group B exemplifies this point, with the overall complication rate dropping from 48% to 20% ($p < 0.005$). We noted a numerical decrease in major complications (18% in group A *vs.* 10% in group B) and a statistically significant reduction in minor complications (30% in group A *vs.* 10% in group B, $p < 0.02$). Interestingly, no complications occurred as a result of the presurgical investigations (*e.g.*, angiography, liver biopsy, or ERCP). Early in the series, many patients were subjected to both angiography and liver biopsies to assess suitability for donation. However, our current protocol requires liver biopsies to be performed on female donors only to evaluate unsuspected steatosis. Angiography is still performed in all patients to delineate arterial anatomy that may preclude donation.

Further analysis of these data demonstrates that LL resections have a significantly higher major complication rate than LLS resections. Fifty-five percent of all LL resections resulted in a major complication *versus* only 10% of LLS resections.

Technical refinements of the procedure have included transecting the left hepatic duct close to the parenchyma and avoiding dissection at the confluence of the right and left hepatic ducts. This refinement should help to reduce the incidence of biliary complications in the donor. The same principle has been applied to the left hepatic artery, which is cut short, thus avoiding dissection at the confluence of the right and left hepatic arteries. Subsequent arterial reconstruction using the operating microscope should decrease the risk of arterial injury in the donor by reducing the length of donor artery required for reconstruction.

Another adjunct to donor safety has been the significant reduction in exposure to heterologous blood products. Only one donor in group B required a heterologous blood transfusion compared with four donors in group A. This may be related to improved surgical technique and reduced surgical time. The technical refinements described above, combined with familiarity with the procedure, have significantly reduced the overall incidence of complications, the surgical time, and the hospital stay.

The data presented suggest that although the procedure is safe, many living donors will have a perisurgical complication. In our series, most of these complications were minor and had no long-term sequelae. Major complications, although significant, did not result in either death or long-term sequelae. Technical modifications and the avoidance of full LL resections have reduced the incidence of major complications, shortened the surgical time, and reduced the hospital stay.

Our data suggest that LDLT should be performed by surgeons experienced in the procedure, and that the use of

LL resections for LDLT should be chosen with caution because they are associated with higher complication rates than LLS resections.

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